Epitomes

Important Advances in Clinical Medicine

Allergy and Immunology

Daniel C. Adelman, MD, and Alan Goldsobel, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association, and the summaries were prepared under the direction of Drs Adelman and Goldsobel and the panel.

Steroid-Resistant Asthma

RECENT STUDIES demonstrate the importance of airway inflammation and immune activation in the pathogenesis of asthma. Glucocorticoids are the most potent anti-inflammatory therapy commonly used in this disease. Certain patients with asthma in whom occult sinusitis, gastroesophageal reflux disease, and environmental allergen exposure have been excluded still fail to have a satisfactory response even to combined inhaled and parenteral glucocorticoid therapy, and their asthma is considered "steroid-resistant." Many of these patients continue treatment with glucocorticoids despite having serious adverse effects and poor clinical response. It is important to differentiate these patients early because they may benefit from alternative approaches to treatment.

Patients with a morning baseline (before bronchodilator use) forced expiratory volume in one second (FEV_1) of less than 70% of the predicted value have steroid-resistant asthma if their morning prebronchodilator FEV_1 value fails to improve by 15% or more after a two-week course of oral prednisone (40 mg per day). In contrast, people whose asthma is steroid-sensitive and who have similar baseline FEV_1 values frequently will have an increased FEV_1 by 30% or greater after prednisone treatment. Patients with a history of steroid resistance should be carefully assessed for misdiagnosis, poor inhaler technique, noncompliance to medications, pharmacokinetic abnormalities in steroid absorption or elimination, persistent allergen exposure, or psychological disorders. Even after these confounding factors in asthma therapy are excluded, a small subset of patients remain whose asthma is poorly responsive to steroid use.

Studies of the peripheral blood and bronchoalveolar lavage (BAL) cells from patients with asthma reveal the presence of persistent eosinophilia and T-cell activation despite treatment with high-dose prednisone. Furthermore, BAL cells from the airways of patients with steroid-resistant asthma have a distinct pattern of cytokine gene expression and response to prednisone that differs from those found in patients with steroid-resistant asthma. Both before and after prednisone therapy, BAL cells from patients with steroid-resistant asthma have a substantially higher level of interleukin (IL)-2 and IL-4 gene expression than BAL cells from those with steroid-sensitive asthma.

Although there is a spectrum of glucocorticoid receptor-binding abnormalities in all patients with chronic asthma, patients with steroid-resistant asthma have the most extreme abnormality in their glucocorticoid receptors. Most patients with steroid-resistant asthma present with severe side effects from parenteral steroid therapy and a lack of benefit. Furthermore, their morning cortisol levels are generally suppressed by steroid therapy. T cells from most of these patients have a glucocorticoid receptor-binding defect that reverses in culture. This "type 1" defect is sustained in vitro by the presence of the combination of IL-2 and IL-4 and is thought to be an acquired defect. A second, less common group of patients with steroid-resistant asthma present with a history of no side effects from high-dose steroid therapy. These patients have normal glucocorticoid receptor-binding affinity but a markedly reduced number of glucocorticoid receptors per cell. The glucocorticoid receptor abnormality in "type 2" steroid-resistant asthma is irreversible and does not respond to coincubation with a combination of IL-2 and IL-4. These patients seem to have a primary steroid resistance syndrome.

Most patients with steroid-resistant asthma have the acquired form of this disorder. A number of factors can contribute to the development of steroid resistance. The overuse of certain drugs, particularly inhaled β-agonists, can reduce steroid responsiveness. Inflammation and immune activation are likely to play a key role in altering glucocorticoid receptor binding and, therefore, steroid responsiveness. In this regard, cytokines can induce transcription factors that directly interact with glucocorticoid receptors and interfere with their ability to bind to DNA.